PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing *(day/month/year)*	16 SEP 1999

Applicant's or agent's file reference	IMPORTANT NOTIFICATION
0973/2D255-W	

International application No.	International filing date *(day/month/year)*	Priority Date *(day/month/year)*
PCT/US98/10719	22 MAY 1998	23 MAY 1997

Applicant
BIOARRAY SOLUTIONS LLC

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II f the PCT Applicant's Guide.

Name and mailing address of the IPEA/US	Authorized officer
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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 0973/2D255-W	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US98/10719	International filing date *(day/month/year)* 22 MAY 1998	Priority date *(day/month/year)* 23 MAY 1997
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant BIOARRAY SOLUTIONS LLC		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets.

   [✓] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 31 sheets.

3. This report contains indications relating to the following items:

   I [X] Basis of the report

   II [ ] Priority

   III [ ] Non-establishment of report with regard to novelty, inventive step or industrial applicability

   IV [ ] Lack of unity of invention

   V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   VI [ ] Certain documents cited

   VII [ ] Certain defects in the international application

   VIII [ ] Certain observations on the international application

Date of submission of the demand	Date of completion of this report
23 DECEMBER 1998	10 AUGUST 1999
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer P. Ponnaluri Telephone No. (703) 308-0196 JOYCE BRIDGERS PARALEGAL SPECIALIST CHEMICAL MATRIX

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US98/10719

I. Basis of the report

1. This report has been drawn on the basis of *(Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments)*:

☐ the international application as originally filed.

☒ the description, pages (See Attached) , as originally filed.
pages _____ , filed with the demand.
pages _____ , filed with the letter of _____.
pages _____ , filed with the letter of _____.

☒ the claims, Nos. (See Attached) , as originally filed.
Nos. _____ , as amended under Article 19.
Nos. _____ , filed with the demand.
Nos. _____ , filed with the letter of _____.
Nos. _____ , filed with the letter of _____.

☒ the drawings, sheets/~~fig~~ (See Attached) , as originally filed.
sheets/~~fig~~ _____ , filed with the demand.
sheets/~~fig~~ _____ , filed with the letter of _____.
sheets/~~fig~~ _____ , filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☒ the description, pages NONE.

☒ the claims, Nos. NONE.

☒ the drawings, sheets/~~fig~~ NONE.

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the ~~Supplemental Box~~ Additional observations below (Rule 70.2(c)).

4. Additional observations, if necessary:

NONE

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US98/10719

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	(Please See supplemental sheet)	YES
	Claims	(Please See supplemental sheet)	NO
Inventive Step (IS)	Claims	(Please See supplemental sheet)	YES
	Claims	(Please See supplemental sheet)	NO
Industrial Applicability (IA)	Claims	(Please See supplemental sheet)	YES
	Claims	(Please See supplemental sheet)	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-16, 18, 22, 24, 30-35, 37-55, 57, 61 and 67-71, lack novelty under PCT Article 33(2) as being anticipated by Ohlmeyer et al. or US Patent 5,565,324 (Still et al).

Ohlmeyer et al teach complex synthetic chemical libraries indexed with inert chemical tags. The reference discloses that a peptide combinatorial library having 117,649 different members, synthesized on beads and indexed with inert chemical tags. The reference teaches that the library was synthesized by first preparing the constant segment of the library on polystyrene beads, using standard solid-phase method based on tBu side chain protection, and Fmoc main chain protection. After removing N-terminal Fmoc protecting group, the beads were divided into fractions and attached the first tag and the corresponding amino acid to each fraction. After washing the fractions were combined, and deprotected, and the beads were divided into fractions again and these steps were repeated several times. To verify that the codes correspond to the actual peptide sequence present on the beads, two beads were picked at random, the tags present on each were released and read by ECGC, and the peptide sequence present on each bead was determined by microseqencing. To pick out the members of library that bound to anti-c-MYC mAb, the bead library was mixed with antibody and stained those beads that bound antibody by using alkaline phosphatase coupled secondary antibodies. The reference also teaches that these methods can be applied to other library types. The reference clearly anticipates the claimed invention.

Claims 1-16, 18, 22, 24, 30-35, 37-55, 57, 61 and 67-71 lack novelty under PCT Article 33(2) as being anticipated by WO 93/06121 (AFFYMAX TECHNOLOGIES N.V.).

AFFYMAX TECHNOLOGIES N.V. teach instruments and method of synthesizing diverse collections of oligomers and the use of identifiers on the oligomers facilitate identification of oligomers with desired properties. The reference teaches that the oligomers are synthesized on solid supports, and the oligomers composed of amino acids, carbamates, sulfones, sulfoxides, nucleosides, (Continued on Supplemental Sheet.)

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

CLASSIFICATION:
The International Patent Classification (IPC) and/or the National classification are as listed below:
IPC(6): C12Q 1/00, 1/68; G01N 21/00, 21/76, 33/53, 33.533, 33/543, 33/566 and US Cl.: 435/4, 6, 7.1, 7.8, 808, 968, 973; 436/501, 518, 546, 164, 172, 800, 805, 807

I. BASIS OF REPORT:

This report has been drawn on the basis of the description,
pages, 1-26, as originally filed.
pages, NONE, filed with the demand.
and additional amendments:
NONE

This report has been drawn on the basis of the claims,
numbers, **NONE** . as originally filed.
numbers, **NONE** as amended under Article 19.
numbers, NONE, filed with the demand.
and additional amendments:
Claims 1-72, filed with the letter of 28 June 1999.

This report has been drawn on the basis of the drawings,
sheets, 1-9, as originally filed.
sheets, NONE, filed with the demand.
and additional amendments:
NONE

V. 1. REASONED STATEMENTS:
The report as to Novelty was positive (YES) with respect to claims 17, 19-21, 23, 25-29, 36, 56, 58-60, 62-66 and 72.
The report as to Novelty was negative (NO) with respect to claims 1-16, 18, 22, 24, 30-35, 37-55, 57, 61 and 67-71.
The report as to Inventive Step was positive (YES) with respect to claims 17, 19-21, 23, 25-29, 36, 56, 58-60, 62-66 and 72.
The report as to Inventive Step was negative (NO) with respect to claims 1-16, 18, 22, 24, 30-35, 37-55, 57, 61 and 67-71.
The report as to Industrial Applicability was positive (YES) with respect to claims 1-72.
The report as to Industrial Applicability was negative (NO) with respect to claims NONE.

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):
carbohydrates, ureas, phosphonates, lipids, esters, combinations of the same and the like. The identifier tag may be composed of a set of light addressable compounds, such as fluorescent or phosphorescent compounds. The oligomer sequence is synthesized in a process comprising : a) apportioning the supports in a stochastic manner among a plurality of reaction vessels; b) exposing the supports in each reaction vessel to a first monomer and to a first identifier; c) pooling the supports; d) apportioning the supports in a stochastic manner among a plurality of reaction vessels; e) exposing the supports in each reaction vessel to a second monomer and a second identifier; and f)repeating steps a) through e) from at least one to twenty times. The reference clearly anticipates the claimed invention.

The amendments and arguments filed on 28 June 1999 have been fully considered and entered into the application. Applicants argue that Still et al (US Patent 5,565,325) or Ohlmeyer et al method requires removal of tag from the bead for analysis and the instant invention does not require off chemical analysis for determining the tag sequence which is determined by direct interrogation. However, the instant claims do not recite the limitation. Still et al or Ohlmeyer et al do not teach the specific fluorophores and the apparatus for identifying compound having selected property of interest in a library of compounds and these claims are withdrawn from the objection.

Applicants arguments regarding the objection of claims over AFFYMAX TECHNOLOGIES N.V. have been considered but are not persuasive. Applicants argue that the present invention differs from AFFYMAX TECHNOLOGIES N.V. and AFFYMAX TECHNOLOGIES N.V. do no disclose optical interrogation for identification of the sequence of a bead as taught by the present disclosure. Applicants arguments have been considered but are not persuasive. AFFYMAX TECHNOLOGIES N.V. teach that the beads bearing the immobilized receptor and sort the beads using FACS to identify positives (diminished fluorescence) or one can determine the fluorescence emitting from the well surface coated with receptor,

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

and the associated identifier tag may be then amplified and decoded. Thus, AFFYMAX TECHNOLOGIES N.V. anticipates the claimed invention.

---------- NEW CITATIONS ----------

OHLMEYER, M.H. et al. Complex Synthetic Chemical Libraries Indexed with Molecular Tags. Proc. Natl. Acad. Sci. USA. December 1993. Vol. 90. pages 10922-10926.

What is Claimed is:

1. A method of identifying a compound having a selected property of interest in a library of compounds, each of said compounds being bound to its respective solid support, and being produced by a unique reaction series composed of *N* reaction steps, wherein each compound is prepared from a component, and *N* is an integer from at least 1 to about 100, which comprises:

   a) dividing a population of solid supports having at least one type of a first functional group at the surface of said solid support selected from the group consisting of CO_2H, OH, SH, NH_2, NHR, CH_2Cl, CH_2Br and CHN_2, wherein R is a linear C_1-C_9 alkyl group, into *M* batches, wherein *M* is an integer from at least 2 to about 25;

   b) coupling the *M* batches of solid support in a set of at least one reaction respectively with *M* different components so as to form a bond with the solid support via said first functional group, said components being independently protected or unprotected;

   c) adding to each batch, either prior to coupling step b), concurrently therewith, or subsequently to step b), from about 0.001 to about 0.5 molar equivalent of a spectrally distinguishable fluorophore tag associated uniquely with each component, said tag being identified by its characteristic excitation wavelength(s), emission wavelength(s), excited state lifetime and emission intensity, said tag being activated so as to be capable of forming either a direct bond to the surface of the solid support, either via the first or a second functional group which is protected or unprotected and is the same as or different from the first functional group bonded to the component, or an indirect bond via a C_1-C_9 linear or branched alkyl linker moiety which is either interrupted or uninterrupted by at least one oxygen or nitrogen atom or a carbonyl, (C=O)NH or

NH(C=O) moiety, wherein when said second functional group is protected, said functional group is deprotected prior to forming said direct or indirect bond, said linker being bonded to the second functional group at the surface of the solid support; and either

d) recombining all *M* batches, said recombining step being either prior to or subsequent to step e) and steps e) - g); or

e) performing an assay capable of indicating that any compound in the library either while bound to or cleaved from its solid support has the property of interest;

f) collecting spectral fluorescence data for each respective solid support so as to determine respective relative abundances of the fluorophore tags bound thereto; and

g) analyzing the collected spectral fluorescence data by comparing the respective relative abundances of the fluorophore tags determined in step f) so as to determine the unique reaction series for the compound, thereby identifying the compound having the property of interest.

2. The method of claim 1 wherein the components are independently selected from the group consisting of an amino acid, a hydroxyacid, an oligoamino acid, an oligopeptide, a saccharide, an oligosaccharide, a diamine, a dicarboxylic acid, an amine-substituted sulfhydryl, a sulfhydryl-substituted carboxylic acid, an alicyclic, an aliphatic, a heteroaliphatic, an aromatic and a heterocyclic moiety.

3. The method of claim 2 wherein the saccharide is a suitably protected D- or L-glucose, fructose, inositol, mannose, ribose, deoxyribose or fucose.

4. The method of claim 2 wherein the oligopeptide is an enkephalin, a vasopressin, an oxytocin, an atrial natrietic factor, a bombesin, a calcitonin, a parathyroid hormone, a neuropeptide Y or an endorphin, or a fragment thereof

comprising at least 20% of the components thereof, or an isosteric analogue thereof wherein independently NH(C=O) is replaced by NH(C=O)NH, NH(C=O)O,CH_2(C=O) or CH_2O; NH_2 is replaced by OH, SH, NO_2 or CH_3; CH_3S is replaced by CH_3 (S=O) or CH_3 CH_2; indole is replaced by naphthyl or indene; hydroxyphenyl is replaced to tolyl, mercaptophenyl or nitrophenyl; and/or hydrogen in an aromatic ring is replaced by chlorine, bromine, iodine or fluorine; C_1-C_4 alkyl is replaced by partially or fully flourinated C_1-C_4 alkyl.

5. The method of claim 2 wherein the oligopeptide is an ACE inhibitor, an HIV protease inhibitor, a cytolytic oligopeptide or an antibacterial oligopeptide.

6. The method of claim 2 wherein the aromatic is para-disubstituted benzene, biphenyl, naphthalene or anthracene, either substituted or unsubstituted by linear or branched chain lower alkyl, alkoxy, halogen, hydroxy, cyano or nitro.

7. The method of claim 2 wherein the heterocyclic moiety is 2,6-disubstituted pyridine, thiophene, 3-7-disubstituted N-protected indole or 2,4-disubstituted imidazole, either substituted or unsubstituted by linear or branched chain lower alkyl, alkyl, halogen, hydroxy, cyano or nitro.

8. The method of claim 1 wherein the solid support is a microsphere, a bead, a resin or a particle, and is composed of a material selected from the group consisting of polystyrene, polyethylene, cellulose, polyacrylate, polyacrylamide, or preferably a silica to glass bead.

9. The method of claim 1 wherein the solid support is chemically modified by covalent attachment of either a substituted or unsubstituted oligo- or polyethyleneglycol, which either terminated or unterminated by an amine substituted by either hydroxymethyl, chloromethyl, aminomethyl or

mercaptomethyl, wherein the functional group at the surface of the solid support is hydroxy, chlorine, NH_2 or SH, respectively.

10. The method of claim 1 wherein the assay is performed while the compound is cleaved from its solid support under conditions whereby the compound remains adsorbed to the solid support.

11. The method of claim 1 wherein the property of interest is binding affinity of a compound to a receptor, the assay is performed by determining a physical response to binding by

a) first admixing with the library of compounds a solution of a labelled receptor so as to result in labelled receptor bound to at least one compound bound to a solid support;

b) removing the solution from the solid support; and either

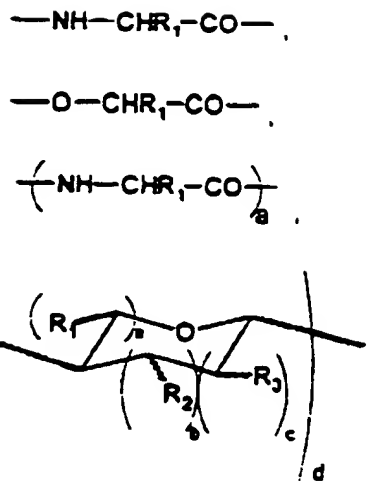
c) washing the solid support so as substantially to remove non-bound labelled receptor, and step (d), or

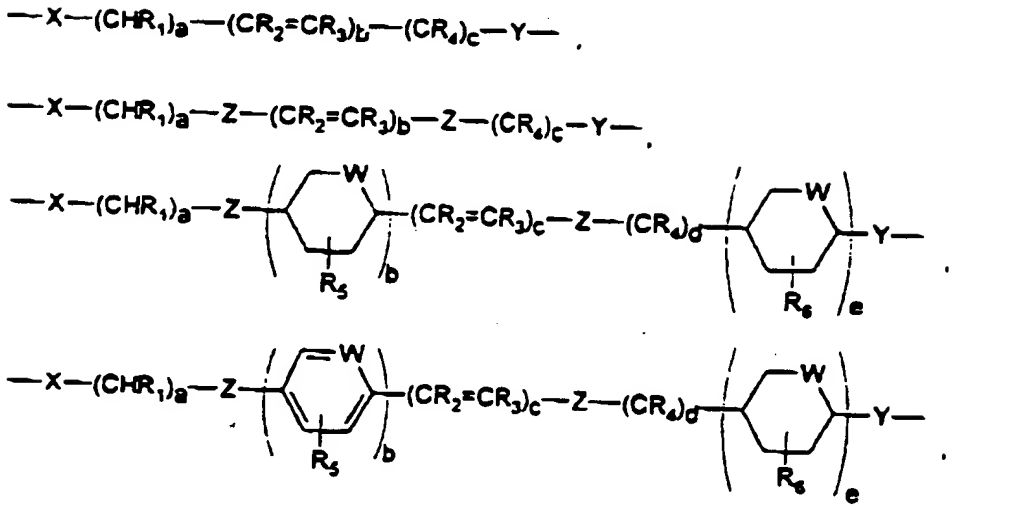
d) measuring the physical response due to bound labelled receptor so as to determine the binding affinity.

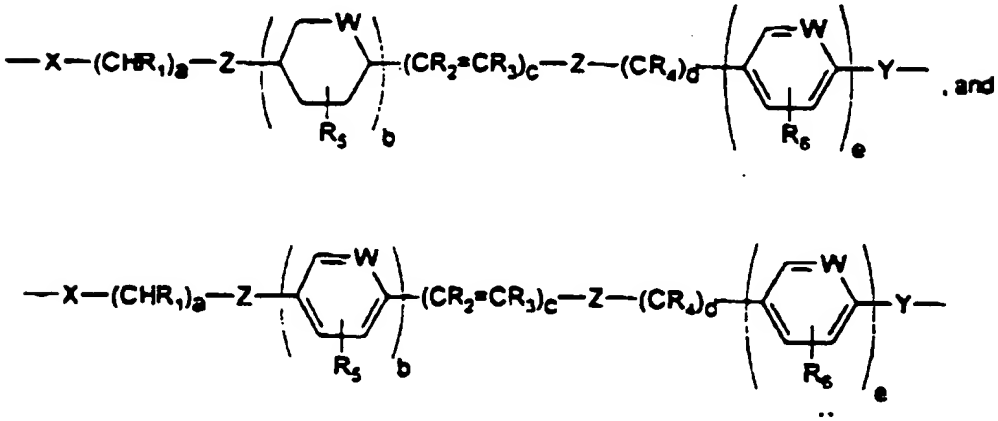
12. The method of claim 11 wherein the receptor is labelled by a fluorescent dye, a colored dye, radioisotope or an enzyme.

13. The method of claim 11 wherein the physical response is fluorescence emission, optical absorption or radioactivity.

14. The method of claim 1 wherein the components have a structure independently selected from the group consisting of:







wherein R_1, R_2, R_3, R_4, R_5 and R_6 are independently methyl, ethyl, linear or branched chain C_3-C_9, phenyl, benzyl, benzoyl, cyano, nitro, halo, formyl, acetyl and linear or branched chain C_3-C_9 acyl; wherein a, b, c, d and e are independently 0, 1, 2 or 3; wherein X, Y and Z are independently NH, O, S, S(=O), CO, (CO)O, O(CO), NH(C=O) or (C=O)NH; and wherein W is independently N, O or S.

15. The method of claim 1 wherein at least one component is an amino acid, bearing a protected or unprotected group which is capable of participating in a further reaction or coupling step and is nitrogen, said protecting group being selected from the group consisting of N-*a*-fluorenylmethyloxcarbonyl, t-butyloxycarbonyl, t-amyloxycarbonyl, (trialkyisilyl) ethyloxycarbonyl, t-butyl and benzyl.

16. The method of claim 1 wherein the fluorophore tag represents a bit of a binary code, and comprises zero, one or more than one fluorescent dye, multiple fluorescent dyes, said dye(s) being spectrally distinguishable by excitation wavelength, emission wavelength, excited-stated lifetime or emission intensity.

17. The method of claim 16 wherein emission intensity is distinguished by adjusting the ration of the relative quantities of each fluorophore.

18. The method of claim 17 wherein the ratio is 1:1, 2:1; 3:1 or 4:1.

19. The method of claim 1 wherein the fluorophore tags are dyes selected from the group consisting of compounds with the chemical names:

3-(ε-carboxypentyl)-3'-ethyl-oxacarbocyanine-6,6'-disulfonic acid

1-(ε-carboxypentyl)-1'-ethyl-3,3,3',3'-tetramethylindocarbocyanine-5,5'-disulfonic acid

1-(ε-carboxypentyl)-1'-ethyl-3,3,3',3'-tetramethyl-3H-benz(e)indocarbocyanine-5,5',7,7'-tetrasulfonic acid

1-(ε-carboxypentyl)-1'-ethyl-3,3,3',3'-tetramethylindocarbocyanine-5,5'-disulfonic acid

1-(ε-carboxypentyl)-1'-ethyl-3,3,3',3'-tetramethyl-3H-benz(e)indodicarbocyanine-5,5',7,7'-tetrasulfonic acid

1-(ε-carboxypentyl)-1'-ethyl-3,3,3',3'-tetramethylindotricarbocyanine-5,5'-disulfonic acid

and are activated as active esters selected from the group consisting of succinimidyl, sulfosuccinimidyl, p-nitrophenol, pentafluorophenol, HOBt and N-hydroxypiperidyl.

20. The method of claim 1 wherein the fluorophore tags are dyes selected from the group consisting of compounds with the chemical names:

6-((4,4-difluoro-5,7-dimethyl- 4-bora-3a,4a-diaza-s-indacene-3-propionyl)amino) hexanoic acid

6-((4,4-difluoro-5-phenyl-4-bora-3a,4a-diaza-s-indacene-3-propionyl) amino) hexanoic acid,

6-((4,4-difluoro-1,3-dimethyl-5-(4-methoxyphenyl)-4-bora-3a, 4a-diaza-s-indacene- 2-propionyl) amino)hexanoic acid,

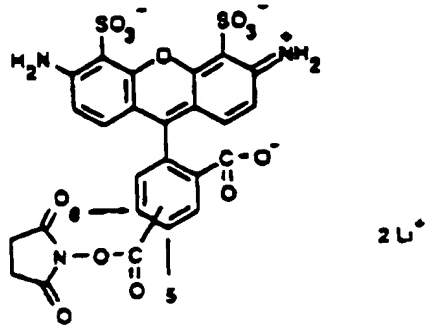
6-(((4-(4,4-difluoro-5-(2-thienyl)-4-bora-3a,4a-diaza-s-indacene-3-yl) phenoxy) acetyl) amino)hexanoic acid,

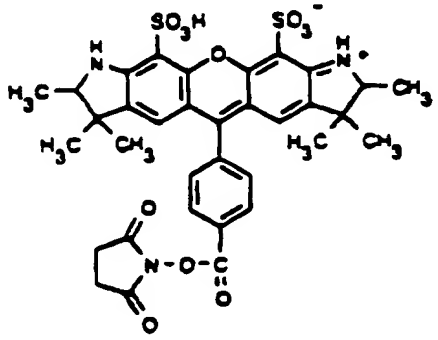
6-(((4,4-difluoro-5-(2-thienyl)-4-bora-3a,4a-diaza-s-indacene-3-yl) styryloxy)acetyl) aminohexanoic acid, and

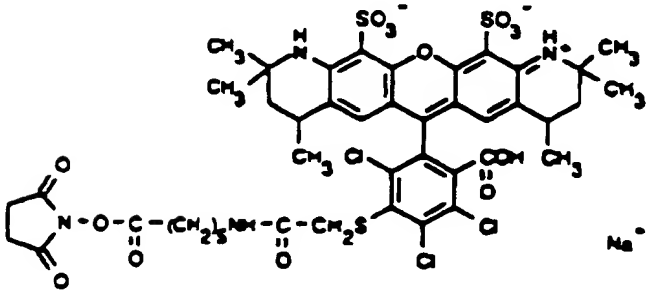
6-(((4,4-difluoro-5-(2-pyrrolyl)-4-bora-3a,4a-diaza-s-indacene-3-yl) styryloxy) acetyl)aminohexanoic acid,

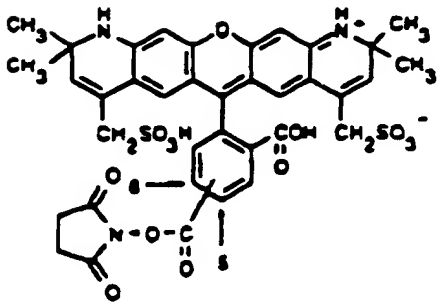
and are activated as active esters selected from the group consisting of succinimidyl, sulfosuccinimidyl, p-nitrophenol, pentafluorophenol, HOBt and N-hydroxypiperidyl.

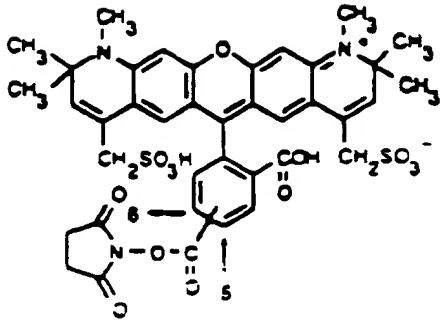
21. The method of claim 1 wherein the fluorophore tags are dyes selected from the group consisting of compounds with the chemical structures:











and are activated as active esters selected from the group consisting of succinimidyl, sulfosuccinimidyl, p-nitrophenol, pentafluorphenol, HOBt and N-hydroxypiperidyl.

22. The method of claim 1 wherein the assay is performed by cleaving compounds from the solid support while permitting diffusion through solution and binding to receptors, said receptors being arranged in proximity to each solid support.

23. The method of claim 1 wherein the fluorescence data are collected from multiple solid supports using multi-spectral imaging methods.

24. The method of claim 1 wherein one of the fluorophore tags uniquely associated with a preselected component or reaction comprises a ligand and a substance capable of binding specifically to the ligand, said ligand being labelled with a fluorophore and attached in a post-assay reaction, said substance being present on the solid support and attached prior to, concurrently with, or subsequent to the coupling of the component, whereby the labelled ligand when bound to the substance indicates the presence of the preselected component.

25. The method of claim 1 wherein the solid support is a polymeric bead, and spectral fluorescence data is collected by

a) forming either a static planar array or a dynamic planar array of beads; and

b) obtaining a fluorescence image for each bead.

26. The method of claim 25 wherein the planar array of beads is formed adjacent to the planar walls of a sandwich flow cell and controlled by light-controlled electrokinetic means.

27. The method of claim 25 wherein the planar array of beads is formed by using an apparatus capable of dynamically assembling and dissembling an array of beads at an interface between an electrode and an electrolyte solution, said apparatus comprising:

i) an electrode, an electrolyte solution and an interface therebetween

ii) a plurality of beads located in said electrolyte solutions;

iii) said electrode being patterned to include at least one area of modified electrochemical properties;

iv) an illumination source which illuminates said electrode with a predetermined light pattern;

v) an electric field generator which generates an electric field at said interface to cause the assembly of an array of beads in accordance with the predetermined light pattern and the electrochemical properties of said electrode; and

vi) an electric field removal unit which removes said electric field to cause the dissembly of said array of beads.

28. The method of claim 25 wherein spectral fluorescence data are collected for the bead array by initially forming a spatially encoded array of beads

being produced by a unique reaction series composed of *N* coupling or reaction steps, wherein each compound is prepared from components which are independently the same or different, and *N* is an integer from at least 1 to about 100, which comprises:

a) dividing a population of solid supports having at least one type of a first functional group at the surface of said solid support surface selected from the group consisting of CO_2H, OH, SH, NH_2, NHR, CH_2Cl, CH_2Br and CHN_2, wherein R is a linear C_1-C_9 alkyl group, into *M* batches, wherein *M* is an integer from at least 2 to about 50;

b) coupling the *M* batches of solid support in a set of at least one reaction respectively with *M* different initial components so as to form a bond with the solid support via said first functional group, said components being optionally protected at a group which is capable of participating in a further coupling step and orthogonally protected at non-participating group(s);

c) adding to each batch optionally prior to coupling step b), concurrently therewith, or subsequently to step b), from about 0.001 to about 0.5 molar equivalent of a spectrally distinguishable fluorophore tag associated uniquely with each initial component or a reaction of step b), said tag being identified by its characteristic excitation wavelength(s), emission wavelength(s), excited state lifetime and emission intensity, said tag being activated so as to be capable of forming either a direct bond to the surface of the solid support, optionally via a second functional group which is optionally protected and may be the same as or different from said first functional group, a direct bond to the initial component which if protected is priorly deprotected, or an indirect bond via a C_1-C_9 linear or branched alkyl linker moiety which is optionally interrupted by at least one oxygen or nitrogen atom or a carbonyl, (C=O)NH or NH(C=O) moiety, said linker being bonded to said first functional group at the surface of the solid support, wherein when said second functional group is protected, said second functional group is deprotected prior to forming said direct or indirect bond;

d) optionally recombining all *M* batches and cleaving any protecting group present at a group which is to participate in a further coupling step, said recombining step optionally being subsequent to step e);

e) iteratively *N* - *1* times

maintaining each of said *mxn* bead arrays in one of the corresponding *mxn* compartments.

29. The method of claim 28, wherein said compartments are hydrophilic and the remainder of said electrode surface is hydrophobic.

30. The method of claim 1 wherein *N* is an integer from at least 2.

31. The method of claim 1 wherein *N* is an integer from at least 4 to about 12.

32. The method of claim 1 wherein *M* is an integer from at least 4 to about 10

33. The method of claim 1 wherein from about 0.01 to about 0.05 molar equivalent of a spectrally distinguishable fluorophore tag is added in step c).

34. A compound having a selected property of interest as identified in accord with claim 1.

35. A chemical library prepared in accord with claim 1.

36. An apparatus for identifying a compound having a selected property of interest in a library of compounds, each of said compounds being bound to its respective solid support, and being produced by a unique reaction series composed of *N* reaction steps, wherein each said compound is prepared from a component, and *N* is an integer from at least 1 to about 100, said solid support being at least one particle array, said apparatus comprising:

a) an electrode and an electrolyte solution having an interface therebetween,

b) an electric field generator which generates an electric field at an interface between an electrode and an electrolyte solution;

c) said electrode being patterned to modify the electrochemical properties of said electrode;

d) an illuminating source which illuminates said interface with a predetermined light pattern to control the movement of said particles in accordance with said predetermined light pattern and the electrochemical properties of said electrode;

e) means for preparing said chemical library, which comprises:

i) means for dividing a population of solid supports having at least one type of a first functional group at the surface of said solid support selected from the group consisting of CO_2H, OH, SH, NH_2, NHR, CH_2Cl, CH_2Br and CHN_2, wherein R is a linear C_1-C_9 alkyl group, into *M* batches, wherein *M* is an integer from at least 2 to about 25;

ii) means for coupling the *M* batches of solid support in a set of at least one reaction respectively with *M* different components so as to form a bond with the solid support via said first functional group, said components being independently protected or unprotected;

iii) means for adding to each batch either prior to coupling step ii), concurrently therewith, or subsequently to step ii), from about 0.001 to about 0.5 molar equivalent of a spectrally distinguishable fluorophore tag associated uniquely with each component, said tag being identified by its characteristic excitation wavelength(s), emission wavelength(s), excited state lifetime and emission intensity, said tag being activated so as to be capable of forming either a direct bond to the surface of the solid support, either via the first or a second functional group which is protected or unprotected and is the same as or different from said first functional group, a direct bond to the component which if

protected is priorly deprotected, or an indirect bond via a C_1-C_9, linear or branched alkyl linker moiety which is either interrupted or uninterrupted by at least one oxygen or nitrogen atom or a carbonyl, (C=O)NH or NH(C=O) moiety, wherein when said second functional group is protected, said second functional group is deprotected prior to forming said direct or indirect bond, said linker being bonded to said second functional group at the surface of the solid support; and either

iv) means for recombining all *M* batches, said recombining step either being prior to or subsequent to step v), and steps v)-vii); or;

v) means for performing an assay capable of indicating that any compound in the library either while bound to or cleaved from its solid support has the property of interest;

vi) means for collecting spectral fluorescence data for each respective solid support so as to determine respective relative abundances of the fluorophore tags bound thereto;

vii) means for analyzing the collected spectral fluorescence data by comparing the respective relative abundances of the fluorophore tags determined in step vi) so as to determine the unique reaction series for the compound, thereby identifying the compound having the property of interest.

37. A method of identifying a compound having a selected property of interest in a library of compounds, each of said compounds being bound to its respective solid support, and being produced by a unique reaction series composed of *N* coupling or reaction steps, wherein each compound is prepared from components which are independently the same or different, and *N* is an integer from at least 1 to about 100, which comprises:

a) dividing a population of solid supports having at least one type of a first functional group at the surface of said solid support surface selected from the group consisting of CO_2H, OH, SH, NH_2, NHR, CH_2Cl, CH_2Br and CHN_2, wherein R is a linear C_1-C_9 alkyl group, into *M* batches, wherein *M* is an integer from at least 2 to about 50;

b) coupling the *M* batches of solid support in a set of at least one reaction respectively with *M* different initial components so as to form a bond with the solid support via said first functional group, said components being protected or unprotected at a group which is capable of participating in a further coupling step and orthogonally protected at non-participating group(s);

c) adding to each batch either prior to coupling step b), concurrently therewith, or subsequently to step b), from about 0.001 to about 0.5 molar equivalent of a spectrally distinguishable fluorophore tag associated uniquely with each initial component or a reaction of step b), said tag being identified by its characteristic excitation wavelength(s), emission wavelength(s), excited state lifetime and emission intensity, said tag being activated so as to be capable of forming either a direct bond to the surface of the solid support, either via the first or a second functional group which is protected or unprotected and is the same as or different from said first functional group, a direct bond to the initial component which if protected is priorly deprotected, or an indirect bond via a C_1-C_9 linear or branched alkyl linker moiety which is interrupted or uninterrupted by either at least one oxygen or nitrogen atom or a carbonyl, (C=O)NH or NH(C=O) moiety, said linker being bonded to said first functional group at the surface of the solid support, wherein when said second functional group is protected, said second functional group is deprotected prior to forming said direct or indirect bond; and either

d) recombining all *M* batches and cleaving any protecting group present at a group which is to participate in a further coupling step, said recombining step being either prior to or subsequent to step e), and steps e)-h); or

e) iteratively *N* - 1 times

(1) dividing a population of solid supports into *M(N)* batches, wherein *M(N)* depends on *N* and is an integer from at least 2 to about 25;

(2) coupling the *M(N)* batches of solid support respectively with *M(N)* different components, wherein *M(N)* is the number of batches during the *N*th step, said components being protected or not protected at a group which is capable of participating in a further coupling step and orthogonally protected at a nonparticipating group(s);

(3) adding to each batch either prior to coupling step (2), concurrently therewith, or subsequently to step (2), from about 0.001 to about 0.5 molar equivalent of a spectrally distinguishable fluorophore tag associated uniquely with each component in the *N*th coupling step (2), said tag being identified by its characteristic excitation wavelength(s), emission wavelength(s), excited state lifetime and emission intensity, said tag being activated so as to form either a direct bond to the surface of the solid support, either via a functional group which is protected or not protected and is the same as or different from the functional group bonded to the component, a direct bond to the (*N* - *1*)th component, or an indirect bond via a C_1 -C_9 linear or branched alkyl linker moiety which is optionally interrupted by at least one oxygen or nitrogen atom or a carbonyl, (C=O)NH or NH(C=O) moiety, said linker being bonded to the functional group at the surface of the solid support, wherein when said functional group is protected, said

function group is deprotected prior to forming said direct or indirect bond; and

(4) recombining all *M(N)* batches and cleaving any protecting group present at a group which is to participate in a further coupling step;

so as to form a compound having *N* components;

f) performing an assay capable of indicating that any compound in the library either while bound to or cleaved from its solid support has the property of interest;

g) collecting spectral fluorescence data for each respective solid support so as to determine respective relative abundances of the fluorophore tags bound thereto; and

h) analyzing the collected spectral fluorescence data by comparing the respective relative abundances of the fluorophore tags determined in step g) so as to determine the *N* components coupled in the unique reaction series for the compound, thereby identifying the compound having the property of interest.

38. The method of claim 37 wherein the components are independently selected from the group consisting of an amino acid, a hydroxyacid, an oligoamino acid, an oligopeptide, a saccharide, an oligosaccharide, a diamine, a dicarboxylic acid, an amine-substituted sulfhydryl, a sulfhydryl-substituted carboxylic acid, an alicyclic, an aliphatic, a hecteroaliphatic, an aromatic and a heterocyclic moiety.

39. The method of claim 38 wherein the saccharide is a suitably protected D- r L-glucose, fructose, inositol, mannose, ribose, deoxyribose or fucose.

40. The method of claim 38 wherein the oligopeptide is an enkephalin, a vasopressin, an oxytocin, an atrial natrietic factor, a bombesin, a calcitonin, a parathyroid hormone, a neuropeptide Y or an endorphin, or a fragment thereof comprising at least 20% of the components thereof, or an isosteric analogue thereof wherein independently NH(C=O) is replaced by NH(C=O)NH, NH(C=O)O, CH_2(C=O) or CH_2O; NH_2, is replaced by OH, SH, NO_2 CH_3; CH_3 S is replaced by CH_3 (S=O) or CH_3 CH_2; indole is replaced by naphthyl or indene; hydroxyphenyl is replaced by tolyl, mercaptophenyl or nitrophenyl; and/or hydrogen in an aromatic ring is replaced by chlorine, bromine, iodine or fluorine; C_1-C_4 alkyl is replaced by partially or fully fluorinated C_1,-C_4, alkyl.

41. The method of claim 38 wherein the oligopeptide is an ACE inhibitor, an HIV protease inhibitor, a cytolytic oligopeptide or an antibacterial oligopeptide.

42. The method of claim 38 wherein the aromatic is para-di substituted benzene, biphenyl, naphthalene or anthracene, either substituted or unsubstituted by linear or branched chain lower alkyl, alkoxy, halogen, hydroxy, cyano or nitro.

43. The method of claim 38 wherein the heterocyclic moiety is 2,6-disubstituted pyridine, thiophene, 3,7-disubstituted N-protected indole or 2,4-disubsituted imidazole, either substituted or unsubstituted by linear or branched chain lower alkyl, alkoxy, halogen, hydroxy, cyano or nitro.

44. The method of claim 37 wherein the solid support is a microsphere, a bead, a resin or a particle, and is composed of a material selected from the group consisting of polystyrene, polyethylene, cellulose, polyacrylate, polyacrylamide, or preferably a silica or glass bead.

45. The method of claim 37 wherein the solid support is chemically modified by covalent attachment of a substituted or unsubstituted oligo- or polyethyleneglycol, which is either terminated or unterminated by an amine substituted by either hydroxymethyl, chloromethyl, aminomethyl or mercaptomethyl, wherein the functional group at the surface of the solid support is hydroxy, chlorine, NH_2 or SH, respectively.

46. The method of claim 37 wherein the assay is performed while the compound is attached to its solid support.

47. The method of claim 37 wherein the assay is performed while the compound is cleaved from its solid support under conditions whereby the compound remains adsorbed to the solid support.

48. The method of claim 37 wherein when the property of interest is binding affinity of a compound to a receptor, the assay is performed by determining a physical response to binding by

a) first admixing with the library of compounds a solution of a labelled receptor so as to result in labelled receptor bound to at least one compound bound to a solid support;

b) removing the solution from the solid support; and either

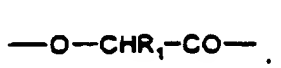
c) washing the solid support so as substantially to remove non-bound labelled receptor, and step (d); or

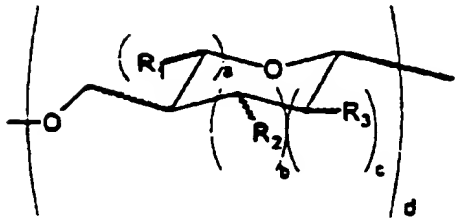
d) measuring the physical response due to bound labelled receptor so as to determine the binding affinity.

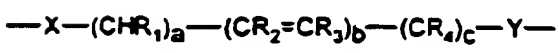
49. The method of claim 48 wherein receptor is labelled by a fluorescent dye, a colored dye, radioisotope or an enzyme.

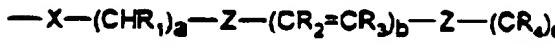
50. The method of claim 48 wherein the physical response is fluorescence emission, optical absorption or radioactivity.

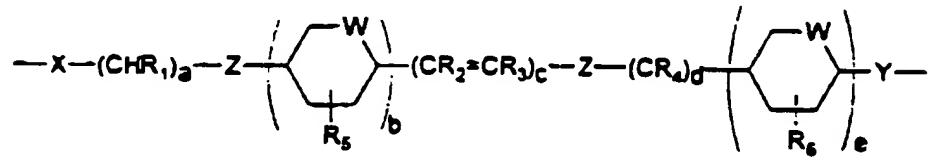
51. The method of claim 37 wherein the components have a structure independently selected from the group consisting of:

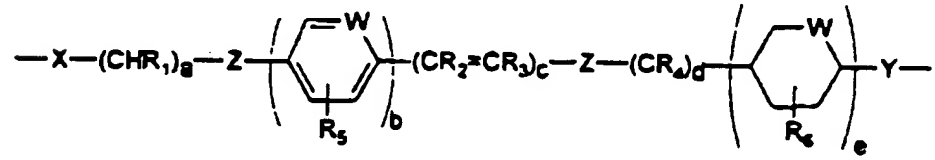


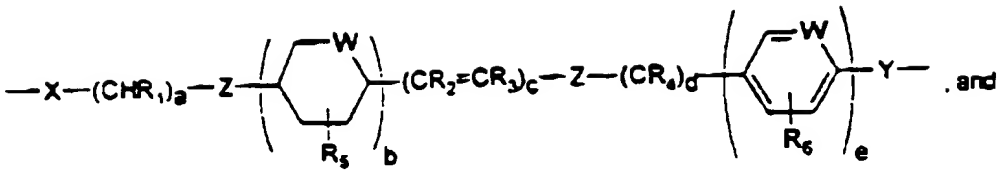


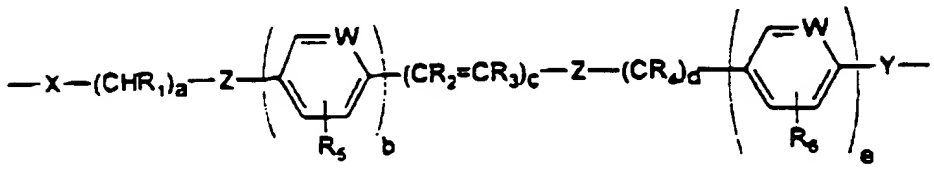












wherein R_1, R_2, R_3, R_4, R_5, and R_6 are independently methyl, ethyl, linear or branched chain C_3-C_9 alkyl, phenyl, benzyl, benzoyl, cyano, nitro, halo, formyl, acetyl and linear or branched chain C_3-C_9 acyl; wherein a, b, c, d and e are independently 0, 1, 2 or 3; wherein X, Y and Z are independently NH, O, S, S(=O), CO, (CO)O, O(CO), NH(C=O) or (C=O) NH; and wherein W is independently N, O or S.

52. The method of claim 37 wherein at least one component is an amino acid, and the protected or unprotected group which is to participate in a further coupling step is nitrogen, said protecting group being selected from the group consisting of N-*a*-fluorenylmethyloxycarbonyl, t-butyloxcarbontyl, t-amyloxycarbonyl, (trialkysilyl) ethyloxycarbonyl, t-butyl and benzyl;

53. The method of claim 37 wherein the fluorophore tag represents a bit of binary code, and comprises zero, one or more than one fluorescence dye, multiple fluorescent dyes, said dye(s) being spectrally distinguishable by excitation wavelength, emission wavelength, excited-state lifetime or emission intensity.

54. The method of claim 37 wherein the assay is performed by cleaving compounds from the solid support while permitting diffusion through solution and binding to receptors, said receptors being arranged in proximity to each solid support.

55. The method of claim 37 wherein the fluorescence data are collected from multiple solid supports using multi-spectral imaging methods.

56. The method of claim 53 wherein emission intensity is distinguished by adjusting the ratio of the relative quantities of each fluorophore.

57. The method of claim 56 wherein the ratio is 1:1, 2:1, 3:1 or 4:1.

58. The method of claim 37 wherein the fluorophore tags are dyes selected from the group consisting of compounds with the chemical names:

3-(ε-carboxypentyl)-3'-ethyl-oxacarbocyanine-6,6'-disulfonic acid

1-(ε-carboxypentyl)-1'-ethyl-3,3,3',3'-tetramethylindocarbocyanine-5,5'-disulfonic acid

1-(ε-carboxypentyl)-1'-ethyl-3,3,3',3'-tetramethyl-3H-benz(e)indocarbocyanine-5,5',7,7'-tetrasulfonic acid

1-(ε-carboxypentyl)-1'-ethyl-3,3,3',3'-tetramethylindocarbocyanine-5,5'-disulfonic acid

1-(ε-carboxypentyl)-1'-ethyl-3,3,3',3'-tetramethyl-3H-benz(e)indodicarbocyanine-5,5',7,7'-tetrasulfonic acid

1-(ε-carboxypentyl)-1'-ethyl-3,3,3',3'-tetramethylindotricarbocyanine-5,5'-disulfonic acid

and are activated as active esters selected from the group consisting of succinimidyl, sulfosuccinimidyl, p-nitrophenol, pentafluorophenol, HOBt and N-hydroxypiperidyl

59. The method of claim 37 wherein the fluorophore tags are dyes selected from the group consisting of compounds with the chemical names:

6-((4,4-difluoro-5,7-dimethyl- 4-bora-3a,4a-diaza-s-indacene-3-propionyl)amino) hexanoic acid

6-((4,4-difluoro-5-phenyl-4-bora-3a,4a-diaza-s-indacene-3-propionyl) amino) hexanoic acid,

6-((4,4-difluoro-1,3-dimethyl-5-(4-methoxyphenyl)-4-bora-3a, 4a-diaza-s-indacene- 2-propionyl) amino)hexanoic acid,

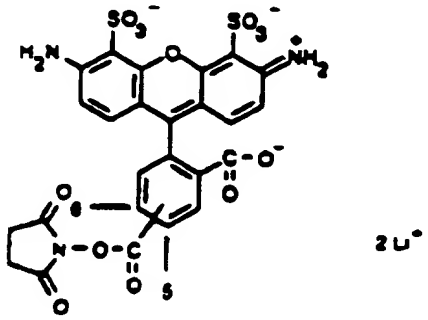
6-(((4-(4,4-difluoro-5-(2-thienyl)-4-bora-3a,4a-diaza-s-indacene-3-yl) phenoxy) acetyl) amino)hexanoic acid,

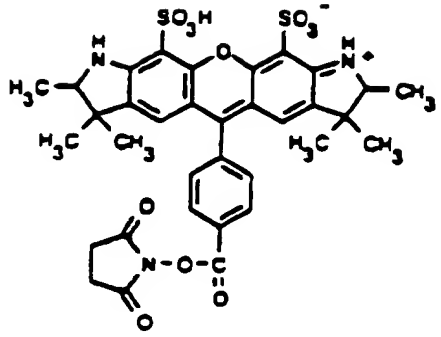
6-(((4,4-difluoro-5-(2-thienyl)-4-bora-3a,4a-diaza-s-indacene-3-yl) styryloxy)acetyl) aminohexanoic acid, and

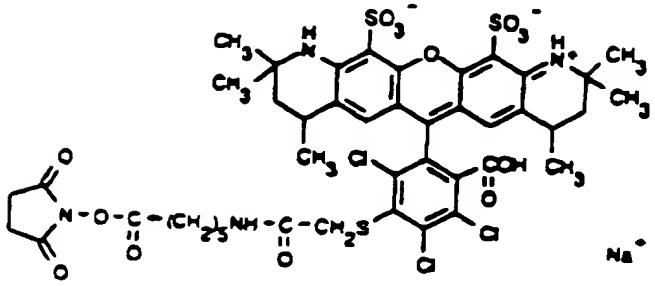
6-(((4,4-difluoro-5-(2-pyrrolyl)-4-bora-3a,4a-diaza-s-indacene-3-yl) styryloxy) acetyl)aminohexanoic acid,

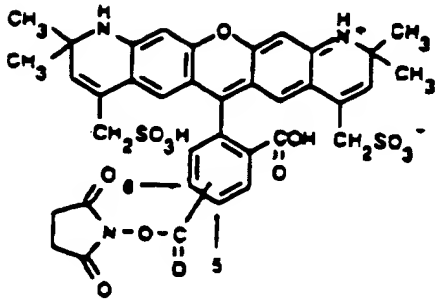
and are activated as active esters selected from the group consisting of succinimidyl, sulfosuccinimidyl, p-nitrophenol, pentafluorophenol, HOBt and N-hydroxypiperidyl.

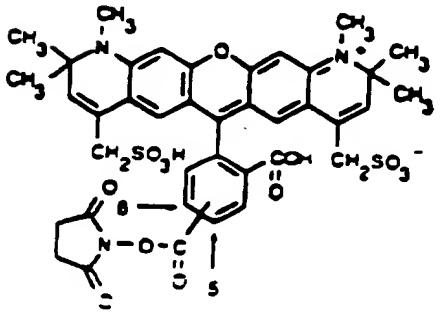
60. The method of claim 37 wherein the fluorophore tags are dyes selected from the group consisting of compounds with the chemical structures:











and are activated as active esters selected from the group consisting of succinimidyl, sulfosuccinimidyl, p-nitrophenol, pentafluorphenol, HOBt and N-hydroxypiperidyl.

61. The method of claim 37 wherein one of the fluorophore tags uniquely associated with a preselected component or reaction comprises a ligand and a substance capable of binding specifically to the ligand, said ligand being labelled with a fluorophore and attached in a post-assay reaction, said substance being present on the solid support and attached prior to, concurrently with, or subsequent to the coupling of the component, whereby the labelled ligand when bound to the substance indicates the presence of the preselected component.

62. The method of claim 37 wherein the solid support is a bead, and spectral fluorescence data are collected by

a) forming either a static planar array or a dynamic planar array of beads; and

b) obtaining a fluorescence image for at least one bead.

63. The method of claim 62 wherein the planar array of beads is formed adjacent to the planar walls of a sandwich flow cell and controlled by light-controlled electrokinetic means.

64. The method of claim 62 wherein the dynamic planar array of beads is formed by using an apparatus capable of dynamically assembling and disassembling an array of beads at an interface between an electrode and an electrolyte solution, said apparatus comprising:

i) an electrode, an electrolyte solution and an interface there between;

ii) a plurality of beads located in said electrolyte solution;

iii) said electrode being patterned to include at least one area of modified electrochemical properties;

iv) an illumination source which illuminates said electrode with a predetermined light pattern;

v) an electric field generator which generates an electric field at said interface to cause the assembly of an array of beads in accordance with the predetermined light pattern and the electrochemical properties of said electrode; and

vi) an electric field removal unit which removes said electric field to cause the disassembly of said array of beads.

65. The method of claim 62 wherein spectral fluorescence data are collected for the bead array by initially forming a spatially encoded array of beads suspended at an interface between an electrode and an electrolyte solution, comprising the following steps:

i) providing an electrode and an electrolyte solution;

ii) providing multiple types of particles, each type being stored in accordance with chemically or physically distinguishable particle characteristics in one of a plurality of reservoirs, each reservoir containing a plurality of like-type particles suspended in said electrolyte solution;

iii) providing said reservoirs in the form of an *mxn* grid arrangement;

iv) patterning said electrode to define *mxn* compartments corresponding to said *mxn* grid of reservoirs;

v) depositing *mxn* droplets from said *mxn* reservoirs onto said corresponding *mxn* compartments, each said droplet originating from one of said reservoirs and remaining confined to one of said *mxn* compartments and each said droplet containing at least one particle;

vi) positioning a top electrode above said droplets so as to simultaneously contact each said droplet;

vii) generating an electric field between said top electrode and said *mxn* droplets;

viii) using said electric field to form a bead array in each of said *mxn* compartments, each said bead array remaining spatially confined to one of said *mxn* droplets;

ix) illuminating said *mxn* compartments on said patterned electrode with a predetermined light pattern to maintain the position of said bead arrays in accordance with said predetermined light pattern and the pattern of *mxn* compartments; and

x) positioning said top electrode closer to said electrode thereby fusing said *mxn* droplets into a continuous liquid phase, while maintaining each of said *mxn* bead arrays in one of the corresponding mxn compartments.

66. The method of claim 65 wherein said compartments are hydrophilic and the remainder of said electrode surface is hydrophobic.

67. The method of claim 37 wherein *N* is an integer from at least 3 to about 12.

68. The method of claim 37 wherein *M* and *M(N)* are independently an integer from at least 4 to about 12.

69. The method of claim 37 wherein from about 0.01 to about 0.05 molar equivalent of a spectrally distinguishable fluorophore tag is added in step c).

70. A compound having a selected property of interest as identified in accord with claim 37.

71. A chemical library prepared in accord with claim 37.

72. An apparatus for identifying a compound having a selected property of interest in a library of compounds, each of said compounds being bound to its respective solid support, and being produced by a unique reaction series composed of *N* coupling and reaction steps, wherein each said compound is prepared from a set of components which are independently the same or different, and N is an integer from at least 1 to about 100, said solid support being at least one particle array, said apparatus comprising:

a) an electrode and an electrolyte solution having an interface therebetween;

b) an electric field generator which generates an electric field at an interface between an electrode and an electrolyte solution;

c) said electrode being patterned to modify the electrochemical properties of said electrode;

d) an illuminating source which illuminates said interface with a predetermined light pattern to control the movement of said particles in accordance with said predetermined light pattern and the electrochemical properties of said electrode;

e) means for preparing said chemical library, which comprises:

i) means for dividing a population of solid supports having at least one type of a first functional group at the surface of said solid support selected from the group consisting of CO_2H, OH, SH, NH_2, NHR, CH_2Cl, CH_2Br and CHN_2, wherein R is a linear C_1-C_9 alkyl group, into *M* batches, wherein *M* is an integer from at least 2 to about 50;

ii) means for coupling the *M* batches of solid support in a set of at least one reaction respectively with M different initial components so as to form a bond with the solid support via said first functional group, said components being protected or unprotected at a group which is

to participate in a further coupling step and orthogonally protected at non-participating group(s);

iii) means for adding to each batch either prior to coupling step ii), concurrently therewith, or subsequently to step ii), from about 0.001 to about 0.5 molar equivalent of a spectrally distinguishable fluorophore tag associated uniquely with each initial component, said tag being identified by its characteristic excitation wavelength(s), emission wavelength(s), excited state lifetime and emission intensity, said tag being activated so as to be capable of forming either a direct bond to the surface of the solid support, either via the first or a second functional group which is protected or unprotected and is the same as or different from said first functional group bonded to the component, or an indirect bond via a C_1-C_9, linear or branched alkyl linker moiety which is either interrupted or uninterrupted by either at least one oxygen or nitrogen atom or a carbonyl, (C=O)NH or NH(C=O) moiety, said linker being bonded to said second functional group at the surface of the solid support, wherein when said second functional group is protected, said second functional group is deprotected prior to forming said direct or indirect bond; and either

iv) means for recombining all *M* batches and cleaving any protecting group present at a group which is to participate in a further coupling step, and steps v)-viii); or

v) means for iteratively *N* - *1* times

(1) dividing a population of solid supports into *M(N)* batches, wherein *M(N)* depends on *N* and is an integer from at least 2 to about 25;

(2) coupling the *M(N)* batches of solid supports respectively with *M(N)* different components, wherein *M(N)* is the number of

batches during the *N*th step, said components being protected or unprotected at a group which is capable of participating in a further coupling step and orthogonally protected at a non-participating group(s);

(3) adding to each batch either prior to coupling step (2), concurrently therewith, or subsequently to step (2), from about 0.001 to about 0.1 molar equivalent of a different spectrally distinguishable fluorophore tag associated uniquely with each component during the *N*th coupling step (2), said tag being uniquely identified by its excitation wavelength, emission wavelength, excited-state lifetime or emission intensity, whereby said tag is activated so as to be capable of forming either a direct bond to the solid support, either via an *N*th functional group which is protected or unprotected and is the same as or different from the first functional group, or an indirect bond thereto via a C_1-C_9 linear or branched alkyl linker moiety which is either interrupted or uninterrupted by either at least one oxygen or nitrogen atom or a carbonyl or NH(C=O) moiety, or a direct bond to the *(N-1)*th component which if protected is priorly deprotected, said tag or linker being bound via the group which is to participate in a further coupling step, wherein when said *N*th functional group is protected, said *N*th functional group is deprotected prior to forming said direct or indirect bond; and

(4) recombining all *M(N)* batches and cleaving the protecting group present if present at a group which is to participate in a further coupling step;

so as to form a compound having *N* components;

vi) means for performing an assay capable of indicating that any compound in the library either while bound to or cleaved from its solid support has the property of interest;

vii) means for collecting spectral fluorescence data for each respective solid support so as to determine respective relative abundances of the fluorophore tags bound thereto;

viii) means for analyzing the collected spectral fluorescence data by comparing the respective relative abundances of the fluorophore tags determined in step vii) so as to determine the *N* components coupled in the unique reaction series for the compound, thereby identifying the compound having the selected property of interest.